JACC: CARDIOONCOLOGY VOL. 1, NO. 1, 2019

EDITORIAL COMMENT

Prokineticin-izing Doxorubicin-Damaged Hearts*

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The cardiotoxicity of anthracyclines such as doxorubicin is a major limitation of this common anticancer treatment, which is especially effective in hematologic, ovarian, and breast malignancies. Patient risk stratification and therapy for this increasingly frequent cardiac condition are still unsatisfactory, and the need for new approaches to anthracycline-induced cardiotoxicity, which can appear years after exposure to doxorubicin, is of great translational interest (1).

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In this issue of *JACC: CardioOncology*, Gasser et al. (2) propose a novel strategy to recover from the cardiac damage induced by doxorubicin, by stimulating cardioprotective signals through the activation of a thus far rather neglected G protein-coupled receptor called PKR1 (or PROKR1). This receptor binds to 2 different peptide agonists, prokineticin 1 and 2, short secreted proteins with hormonal function, linked to gastrointestinal smooth muscle contraction, circadian rhythm regulation, neurogenesis, angiogenesis, pain perception, mood regulation, and reproduction (3). The PKR1 receptor is present in the nervous system and in various mesenchymal cells, including cardiomyocytes and endothelial cells. In the cardiovascular system, signals relayed by PKR1 are known to exert beneficial effects, including insulin sensitization, vasculogenesis, and cell survival (4,5). Nonetheless, PKR1 has a dark-sided relative, PRK2, which also responds to prokineticins but induces cardiomyocyte hypertrophy and endothelial dysfunction, which leads to dilated cardiomyopathy and vascular leakage, respectively (6). Therefore, to explore the possibility of specifically targeting PKR1 to exploit its cardioprotective actions, the Nebigil laboratory recently identified a synthetic peptidomimetic compound called IS20 that specifically and selectively activates PKR1 (7). In vivo, in mouse models of infarction, this peptide was able to protect cardiac function and improve survival (7).

As a natural extension of such findings with PKR1 agonists, the study by Gasser et al. (2) explores the potential cardioprotective action of IS20 in models of doxorubicin-induced cardiotoxicity in vitro and in vivo. Remarkably, IS20 was able to significantly protect different cardiac cell types from the toxic insult of doses of this anthracycline that closely mimicked those received by patients. IS20 not only protected cardiomyocytes and H9c2 cardioblasts but also endothelial cells and epicardium-derived progenitor cells. In vivo, systemic PKR1 activation with intraperitoneal injections of IS20 significantly blunted the long-term effects of doxorubicin and prevented the decline in diastolic ejection fraction seen in vehicle-treated controls. Analysis of survival strikingly showed that systemic treatment with IS20 reduced doxorubicin-induced lethality without disturbing its anticancer activity on either mammary or ovary malignant cell lines.

Elegantly, Gasser et al. (2) show that the effects of IS20 are unequivocally mediated by PRK1-dependent signaling, because IS20 was ineffective in cells with knock down for PRK1 and in PRK1-deficient murine hearts. In addition, this study highlights that the cells most sensitive to doxorubicin and to the protective effect of IS20 are endothelial cells and epicardium-derived progenitor cells. In these cells, doxorubicin

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2019.08.009

accelerates damage by negatively interfering with the regulation of the detoxification program controlled by the transcription factor NRF2 (nuclear factor-like 2), a key activator of antioxidant and antiapoptotic pathways. Gasser et al. (2) show that IS20 counteracts this effect, and whereas doxorubicin leads to nuclear exclusion of NRF2, IS20 restores its nuclear buildup. As an explanation for these observations, Gasser et al. (2) provide substantial evidence that this likely occurs via activation of the phosphoinositide 3-kinase (PI3K)/Akt signaling axis, a well-known trigger of NRF2 nuclear translocation and, at the same time, of antiapoptotic responses such as Bcl2 accumulation.

Interestingly, studies in cancer cells show that the PI3K/Akt pathway is a double-edged sword: although it triggers antioxidant responses, it also stimulates production of reactive oxygen species by activating NADPH oxidases and mitochondrial bioenergetics (8). The sustained PI3K pathway thus allows cancer cells to live and thrive with abnormally increased levels of reactive oxygen species. This is also associated with cancer progression, because this condition can help malignant cells withstand increased oxidative stress, eventually leading to accumulation of DNA damage and cancer-driving mutations. Not surprisingly, hyperactivation of the PI3K signaling pathway is one of the most common events in human cancer (9), and under some conditions, PI3K inhibition can protect the heart against doxorubicin-induced toxicity (10). PI3K signaling is also critically associated with cardiac hypertrophy (11). Although this is likely associated with activation of PI3K isoforms responding to tyrosine kinase receptors and potentially not to G protein-coupled receptors such as PRK1, the downside of potential long-term PI3K hyperactivation in cardiomyocytes should not be underestimated.

The finding by Gasser et al. (2) that IS20 further triggers PI3K/Akt should thus be considered carefully, because it can promote cancer growth as well as cardiomyocyte hypertrophy. Although their study showed that 2 to 3 mammary gland and ovarian tumor cell lines were unresponsive to IS20 and PKR1 activation, such cells might not necessarily represent the vast genomic variability and gene expression diversity of cancers of the breast and ovaries. For example, The Cancer Genome Atlas (TCGA) database, interrogated through cBioPortal, indicates that up to 2% of ovarian and 1% of breast malignancies show PRK1/PROKR1 gene amplification that can likely sensitize them to IS20. Although this unwanted effect of IS20 can be avoided with careful patient stratification, the consequences for cardiomyocytes enduring a persistent PI3K pathway stimulation potentially leading to hypertrophy need to be explored carefully in the future.

Similarly, prokineticin signaling is involved in a myriad of physiological functions, including circadian rhythms, neurogenesis, ingestive behaviors, nociception, and mood regulation. Further studies considering the potential systemic side effects of IS20 are awaited in the near future before the elegant findings of Gasser et al. (2) can be translated to a first-in-human study.

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KEY WORDS cardiotoxicity, doxorubicin, PI3K/Akt pathway, prokineticin